CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-920

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-920

AUG 10 2001

Scios Inc.
Attention: Mr. Michael Crockett
820 West Maude Ave.
Sunnyvale, CA 94085

Dear Mr. Crockett:

Please refer to your new drug application (NDA) dated April 24, 1998, received April 27, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Natrecor (nesiritide) for Injection, 1.5 mg/vial.

We acknowledge receipt of your submissions dated July 18, 26 and 31, and August 9, 2001. Your submission of July 31, 2001 constituted a complete response to our July 6, 2001 approvable letter.

This new drug application provides for the use of Natrecor (nesiritide) for Injection for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert and immediate container and carton labels included in your July 31, 2001 submission). Accordingly, the application is approved effective on the date of this letter.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We acknowledge your request of January 9, 2001 asking for a waiver of the pediatric study requirement for this action on this application. We agree to waive that requirement for this application for all pediatric age groups covered by the Pediatric Rule.

In telephone conversations with Dr. Quynh Nguyen, Division of Cardio-Renal Drug Products, on August 3 and 8, 2001, you agreed to make the following changes to the package insert at the time of your next printing:

1) In the last sentence under **DESCRIPTION/Special Populations**, correct the typographical error "baseline Cl" to "baseline CI".

2) Change the word "Natrecor" to "nesiritide" under the **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection.

3) Change the first two sentences under **PRECAUTIONS/Pregnancy: Category C** to "Animal

developmental and reproductive toxicity studies have not been conducted with nesiritide. It is not known whether Natrecor can cause fetal harm when administered to pregnant women or can affect reproductive capacity."

Please report these labeling changes in your annual report.

We also note that there were minor editorial changes made throughout the package insert.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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JUL -6 2001

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We acknowledge receipt of your submissions dated November 19, 1999, January 14 and June 21, 2000, January 9 and 26 (two), March 1, 26, 28 and 30, April 3 and 20, May 29, June 5, 6, 8 and 29, 2001. Your submission of January 9, 2001 constituted a complete response to our April 27, 1999 not-approvable letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked up draft.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

During a recent inspection of the manufacturing facility for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the investigator. A satisfactory inspection will be required before this application may be approved.

Please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane

Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

/S/

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Marked-up Draft Labeling

17 pages redacted from this section of the approval package consisted of draft labeling